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Prognostic Value of Pacing-Induced Mechanical Alternans in Patients With Mild-to-Moderate Idiopathic Dilated Cardiomyopathy in Sinus Rhythm

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OBJECTIVES The relation between the occurrence of pacing-induced mechanical alternans and prognosis in patients with mild-to-moderate idiopathic dilated cardiomyopathy (IDCM) in sinus rhythm was investigated prospectively. The myocardial expression of genes for Ca^{2+}-handling proteins in such patients was also examined.

BACKGROUND Mechanical alternans occurs in some patients with severe heart failure, but the relation between the occurrence of mechanical alternans and prognosis in patients with IDCM has remained unknown.

METHODS Left ventricular (LV) pressure was measured during atrial pacing, and LV endomyocardial biopsy specimens were collected in 36 IDCM patients and 8 controls. Idiopathic dilated cardiomyopathy patients were divided into two groups consisting of 22 individuals who did not develop mechanical alternans at heart rates up to 140 beats/min (group A) and of 14 individuals who did (group B). The patients were followed up for a mean of 3.7 years.

RESULTS There was no significant difference in LV ejection fraction or the plasma concentration of brain natriuretic peptide between groups A and B. The myocardial abundance of ryanodine receptor 2 messenger ribonucleic acid (mRNA) was significantly lower in groups A and B than in controls, whereas that of sarcoplasmic reticulum Ca^{2+}-ATPase mRNA was significantly lower in group B than in group A or controls. Stepwise multivariate analysis identified pacing-induced mechanical alternans as the strongest predictor of cardiac events. Event-free survival in group A was significantly greater than that in group B.

CONCLUSIONS The occurrence of pacing-induced mechanical alternans is a potentially useful indicator of poor prognosis in patients with mild-to-moderate IDCM in sinus rhythm. (J Am Coll Cardiol 2006;47:1382–9) © 2006 by the American College of Cardiology Foundation

Idiopathic dilated cardiomyopathy (IDCM) is characterized by progressive left ventricular (LV) dilation and greatly impaired LV systolic function, eventually culminating in end-stage congestive heart failure (CHF) and cardiac death (1,2). It is therefore important to identify as early as possible patients with IDCM who are unlikely to improve or stabilize in response to standard medical treatment. Several studies have attempted to find clinical or other abnormalities associated with poor prognosis in such individuals. Markers examined have included indexes related to LV systolic or diastolic function, such as LV ejection fraction (LVEF), LV end-diastolic dimensions and pressures, and the plasma concentration of brain natriuretic peptide (BNP) (2–6). However, LVEF is load-dependent, and plasma BNP level is affected by changes in LV wall stress during treatment (7–9), properties that may limit their predictive value. Furthermore, the plasma concentration of BNP has been found to be less accurate for detection of milder degrees of systolic dysfunction (10), which are more common than are severe forms but are also associated with increased risk of mortality.

Mechanical alternans has been detected in both patients with severe heart failure and animal models of this condition (11–13). Although rare under resting conditions in individuals with controlled heart failure (14), mechanical alternans is more prevalent and likely to be sustained at higher heart rates (15). The relation between the occurrence of mechanical alternans and the prognosis of patients with IDCM has not previously been examined, however.

Atrial fibrillation is common in patients with IDCM and is associated with a variety of potentially deleterious hemodynamic consequences that might exert a negative influence on prognosis and accelerate the progression of LV systolic dysfunction (16). The overall survival rate for patients in sinus rhythm is higher than that for patients with atrial fibrillation (16,17). However, prognostic indicators for pa-

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Abbreviations and Acronyms

BNP	= brain natriuretic peptide
CHF	= congestive heart failure
GAPDH	= glyceraldehyde-3-phosphate dehydrogenase
IDCM	= idiopathic dilated cardiomyopathy
LV	= left ventricle or left ventricular
$LVdP/dt_{max}$	= maximal first derivative of LV pressure
LVEF	= left ventricular ejection fraction
mRNA	= messenger ribonucleic acid
RT-PCR	= reverse transcription-polymerase chain reaction
SERCA2	= sarcoplasmic reticulum Ca^{2+}-ATPase
$T_{1/2}$	= pressure half-time

tients with mild-to-moderate IDCM in sinus rhythm remain unclear. We have therefore now examined prospectively the prognostic value of pacing-induced mechanical alternans in patients with mild-to-moderate IDCM in sinus rhythm.

METHODS

Subjects. We studied 36 patients with mild-to-moderate IDCM (mean age, 49 years; range, 32 to 62 years), 26 of whom had previously been admitted to hospital because of heart failure with dyspnea on exertion, palpitations, or peripheral edema. The remaining 10 patients were asymptomatic and were identified on the basis of an electrocardiogram abnormality at an annual health check. The IDCM of the patients was defined as mild-to-moderate on the basis of clinical symptoms.

All patients showed a normal sinus rhythm; IDCM was defined on the basis of the presence of both a reduced LVEF (<50% as determined by contrast left ventriculography) and a dilated LV cavity in the absence of coronary or valvular heart disease, arterial hypertension, or cardiac muscle disease caused by any known systemic condition (18). None of the patients had an identifiable family history of dilated cardiomyopathy in a second-degree relative. The 26 patients who had previously been hospitalized for acute heart failure were receiving treatment and were in stable condition before their referral to Nagoya University Hospital for cardiac catheterization. The period that elapsed between hospitalization and catheterization averaged 4.0 months (range, 2 to 8 months).

The control subjects consisted of eight individuals undergoing diagnostic cardiac catheterization for evaluation of atypical chest pain and a mild ST-T abnormality on their electrocardiograms. All control subjects manifested normal echocardiograms, coronary arteriograms, and contrast ventriculograms. Endomyocardial biopsies were also performed to exclude myocarditis or specific heart muscle disease, and all control subjects had normal pathological findings. The study protocol was approved by the appropriate institutional review committee, and written informed consent was obtained from all subjects.

Cardiac catheterization. A 6-F fluid-filled pigtail catheter with a high-fidelity micromanometer (model SPC-464D, Millar Instruments, Houston, Texas) was advanced into the LV through the right femoral artery for measurement of LV pressure. A 6-F bipolar pacing catheter was introduced through the right femoral vein and positioned in the right atrium. Right atrial pacing was initiated at 80 beats/min and increased in increments of 10 beats/min. Micromanometer pressure signals and standard electrocardiograms were recorded with a multichannel recorder (MR-40, TEAC, Tokyo, Japan) throughout the procedure. Left ventricular pressure signals were digitized at 3-ms intervals and analyzed with a 32-bit microcomputer system and software developed in-house. We selected steady-state LV pressure data at the baseline and at each pacing rate for analysis. We calculated the maximal first derivative of LV pressure (LV dP/dt_{max}) as an index of contractility. To evaluate LV isovolumic relaxation, we computed the pressure half-time ($T_{1/2}$) directly as previously described (19). The peak pacing rate was defined as the heart rate at which second-degree atrioventricular block occurred. After completion of the pacing study, selective coronary angiography as well as left ventriculography was performed. Endomyocardial biopsy was also performed in all patients to exclude myocarditis or specific heart muscle disease. Several (at least three) endomyocardial biopsy specimens were obtained from the free wall of the LV. Biopsy samples for messenger ribonucleic acid (mRNA) analysis were frozen immediately in liquid nitrogen and stored at −80°C until use.

Quantitative reverse transcription-polymerase chain reaction (RT-PCR) analysis. Quantitative RT-PCR analysis of the amounts of the mRNAs for glyceraldehyde-3-phosphate dehydrogenase (GAPDH), sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2), ryanodine receptor 2, phospholamban, calsequestrin, and the Na^{+}-Ca^{2+} exchanger was performed with a Prism 7700 Sequence Detector (Perkin-Elmer, Foster City, California) as previously described (20). Variability in the efficiency of cDNA synthesis was corrected by dividing the levels of Ca^{2+}-handling protein mRNAs by that of GAPDH mRNA.

Study protocol. To evaluate whether the rate of cardiac events differed between patients with or without pacing-induced mechanical alternans, we prospectively followed up all patients for the occurrence of primary events, which were defined as cardiac death (from worsening CHF or sudden death) or the unscheduled readmission for decompensated CHF. Noncardiac death was excluded.

Statistical analysis. Data are presented as means ± SD. Baseline characteristics and hemodynamic variables were compared among groups by one-way factorial analysis of variance; if a significant difference was detected, intergroup comparisons were performed with Scheffe's multiple-comparison test. Reverse transcription-polymerase chain reaction analysis of the abundance of Ca^{2+}-handling protein mRNAs among groups were also compared by one-way

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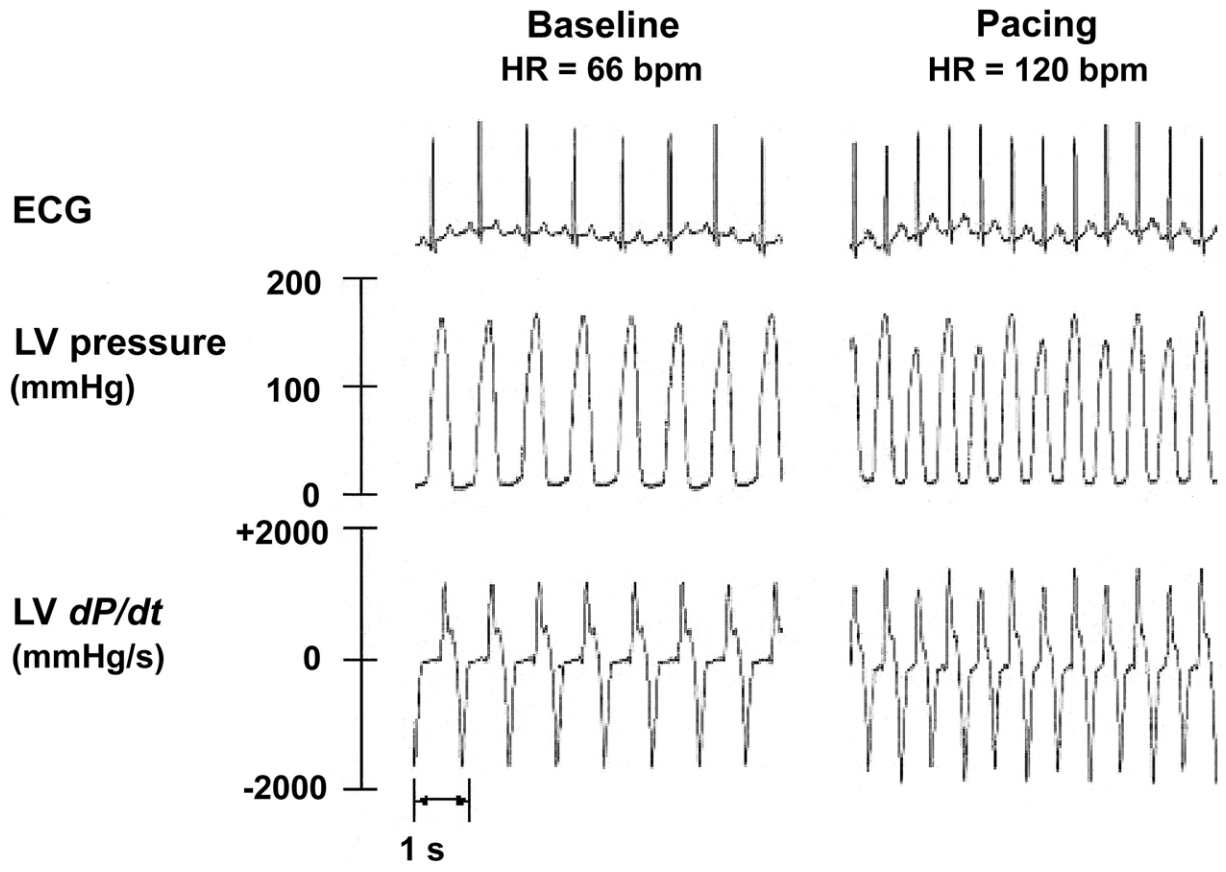

Figure 1. Representative records of pacing-induced mechanical alternans. The **traces** represent a lead II electrocardiogram (ECG), left ventricular (LV) pressure, and LV *dP/dt* at a baseline heart rate (HR) of 66 beats/min (bpm) and at atrial pacing of 120 bpm for a male patient with idiopathic dilated cardiomyopathy. Alternating pressure was 30 mm Hg at the pacing rate of 120 bpm. Both LV dP/dt_{max} and LV dP/dt_{min} showed alternating changes with LV pressure. dP/dt = first derivative of left ventricular pressure.

factorial analysis of variance if a significant difference was detected. Within-group comparisons for changes in hemodynamic variables between baseline and 120 beats/min of atrial pacing were performed with the paired Student *t* test. Comparisons between measurements from the strong and weak beats of mechanical alternans were also performed with the paired Student *t* test. Cox proportional hazard regression analysis was performed to identify independent predictors of cardiac events. We also performed a stepwise forward selection procedure. Cumulative cardiac event estimates were calculated by the Kaplan-Meier method; differences between the survival curves were assessed by the log-rank test. All analyses were performed with the SPSS 12.0 software package (SPSS Inc., Chicago, Illinois). A p value of <0.05 was considered statistically significant.

RESULTS

Classification of IDCM patients based on mechanical alternans. Mechanical alternans was diagnosed if the pressure difference between the strong and weak beats was ≥4 mm Hg. Under baseline conditions, no patient exhibited mechanical alternans. We divided the IDCM patients into two groups on the basis of the absence or presence of pacing-induced mechanical alternans. Group A consisted of 22 IDCM patients who did not develop mechanical alternans at heart rates up to 140 beats/min, whereas group B comprised 14 IDCM patients who did. The average heart rate at which mechanical alternans appeared (critical pacing heart rate) in IDCM patient group B was 99 ± 10 beats/min. Waveforms at baseline and 120 beats/min of pacing for a representative male IDCM patient with pacing-induced mechanical alternans are shown in Figure 1.

Baseline clinical data. Baseline clinical characteristics for the control group and IDCM patient groups A and B are shown in Table 1. There were no significant differences in age or sex among the three study groups. All IDCM patients were classified as New York Heart Association functional class I or II at the time of cardiac catheterization. Of the 36 IDCM patients, 12 had been treated previously with digitalis, 28 with diuretics, 26 with angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, and 19 with beta-blockers. There were no signifcant differences in drug treatment at entry into the study between patient groups A and B. There was also no significant difference in LVEF between groups A and B. The LV end-diastolic and end-systolic volumes were both significantly increased in IDCM patient group B compared with those in group A. The plasma BNP level tended to be

Table 1. Baseline Clinical Characteristics

Characteristics	Controls (n = 8)	IDCM	
		Group A (n = 22)	Group B (n = 14)
Age (yrs)	45 ± 12	48 ± 13	51 ± 12
Gender (M/F)	8/0	20/2	11/3
NYHA functional class			
I		13 (59%)	6 (43%)
II		9 (41%)	8 (57%)
Prior treatment			
Digitalis	0	6 (27%)	6 (43%)
Diuretics	0	16 (73%)	12 (86%)
ACE inhibitors or AR blockers	0	17 (77%)	9 (64%)
Beta-blockers	0	10 (45%)	9 (64%)
LV end-diastolic dimension (mm)	49 ± 5	61 ± 8*	69 ± 9*†
LV end-systolic dimension (mm)	31 ± 5	50 ± 8*	58 ± 9*†
IVS thickness (mm)	10 ± 2	9 ± 2	9 ± 1
LVPW thickness (mm)	10 ± 2	9 ± 2	9 ± 1
LV mass index (g/m^2)	131 ± 38	142 ± 57	172 ± 48
LV end-diastolic volume (ml)	133 ± 45	170 ± 59	253 ± 112*†
LV end-systolic volume (ml)	40 ± 21	108 ± 50	184 ± 90*†
LVEF (%)	66 ± 8	37 ± 9*	33 ± 8*
PAWP (mm Hg)	8 ± 3	9 ± 4	16 ± 9‡§
Cardiac index ($l\ min^{-1}\ m^{-2}$)	3.36 ± 1.41	2.93 ± 0.49	2.70 ± 0.92
Plasma BNP (pg/ml)	6 ± 3	68 ± 69	98 ± 116

*$p < 0.01$ vs. controls; †$p < 0.01$ vs. group A; ‡$p < 0.05$ vs. controls; §$p < 0.05$ vs. group A.
ACE = angiotensin-converting enzyme; AR = angiotensin-II receptor; BNP = brain natriuretic peptide; IDCM = idiopathic dilated cardiomyopathy; IVS = interventricular septum; LV = left ventricular; LVEF = LV ejection fraction; LVPW = LV posterior wall; NYHA = New York Heart Association; PAWP = pulmonary arterial wedge pressure.

higher in group B than in the control group or in group A, but these differences were not significant.

Given that 10 of the 22 patients in group A and 6 of the 14 patients in group B could not achieve a heart rate of >130 beats/min because of Wenckebach block, we compared hemodynamic variables at baseline with those at 120 beats/min of pacing (Table 2). There was no significant difference in LV peak-systolic pressure or LV end-diastolic pressure at baseline among the three groups of subjects; IDCM patients exhibited a lower LV dP/dt_{max} and a longer $T_{1/2}$ than did controls at baseline. There was no significant difference in LV dP/dt_{max} or $T_{1/2}$ between patient groups A and B at baseline.

Abundance of Ca^{2+}-handling protein mRNAs in endomyocardial biopsy specimens. The amounts of Ca^{2+}-handling protein mRNAs in endomyocardial biopsy specimens were determined by RT-PCR analysis and were normalized relative to that of GAPDH mRNA (Table 3). The abundance of SERCA2 mRNA in the LV myocardium was significantly reduced in patient group B compared with that in patient group A or in the control group. The amount of ryanodine receptor 2 mRNA was significantly reduced in patient groups A and B compared with that in the control group. No significant differences in the levels of phospholamban, calsequestrin, or Na^+-Ca^{2+} exchanger mRNAs or in the SERCA2/Na^+-Ca^{2+} exchanger mRNA ratio were apparent among the three groups.

Univariate and multivariate analysis of cardiac events. Univariate analysis revealed that pacing-induced mechanical alternans, heart rate, LV end-diastolic pressure, the ratio of LV end-diastolic pressure to cardiac index, and LVEF were significant predictors of cardiac events (Table 4). These variables were then subjected to stepwise multivariate analysis, yielding only pacing-induced mechanical alternans as a significant independent predictor of cardiac events.

Event-free survival. The cumulative probability of event-free survival was calculated by the Kaplan-Meier method (Fig. 2). All patients with IDCM were followed for an average of 3.7 years (range, 0.8 to 7.5 years) starting at the time of catheterization and ending with a cardiac event or the most recent evaluation of survivors. Two patients (one in each of groups A and B) were excluded from this analysis because they died of noncardiac causes. Cardiac death occurred in one patient in group A and two patients in group B. One patient in group A experienced CHF. Six patients in group B experienced cardiac events, classified as CHF in five and syncope in one. The three-year cumulative probabilities of event-free survival were 88.1% in group A and 40.4% in group B. The probability of event-free survival in group A was significantly higher than that in group B by the log-rank test.

DISCUSSION

We have shown that the occurrence of pacing-induced mechanical alternans was a predictor of poor prognosis in patients with mild-to-moderate IDCM in sinus rhythm, and that the abundance of SERCA2 mRNA in LV endo-

Table 2. Hemodynamic Variables at Baseline and at a Heart Rate of 120 Beats/min During Pacing

Variables	Baseline	Pacing	p Value
Heart rate (beats/min)			
Controls	62 ± 6	120 ± 0	
Group A	* 70 ± 12 †	120 ± 0	
Group B	90 ± 18	120 ± 0	
LVPSP (mm Hg)			
Controls	124 ± 27	119 ± 16	
Group A	121 ± 18	118 ± 18	
Group B	119 ± 20	117 ± 21 (strong) ‡	
		109 ± 20 (weak)	§
LVEDP (mm Hg)			
Controls	9 ± 4	3 ± 3	§
Group A	11 ± 7	7 ± 7	§
Group B	16 ± 10	13 ± 9 (strong) ‡	§
		11 ± 9 (weak)	§
LV dP/dt_{max} (mm Hg/s)			
Controls	1,759 ± 361	2,131 ± 487	§
Group A	* * 1,275 ± 246	* * * 1,411 ± 275	§
Group B	1,145 ± 237	1,291 ± 264 (strong) ‡ ‖	§
		1,148 ± 225 (weak)	§
$T_{1/2}$ (ms)			
Controls	31 ± 2	25 ± 3	
	¶ ¶	¶ ¶ ¶	
Group A	41 ± 9	35 ± 8	§
Group B	42 ± 8	36 ± 8 (strong) ‡	§
		37 ± 8 (weak)	§

*p < 0.01 vs. controls; †p < 0.01 vs. group A; ‡p < 0.01 vs. strong beat at 120 beats/min; §p < 0.01 vs. baseline; ‖p < 0.05 vs. group A; ¶p < 0.05 vs. controls.
LV dP/dt_{max} = maximal first derivate of left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; LVPSP = left ventricular peak systolic pressure; $T_{1/2}$ = pressure half-time.

myocardial biopsy specimens was decreased in IDCM patients with pacing-induced mechanical alternans compared with that in those without it.

Despite recent improvements in the medical management of patients with IDCM, the overall prognosis of such individuals remains poor, with heart transplantation often being the only lifesaving therapeutic option (1,2,6). Even in patients with mild-to-moderate IDCM, sudden death occasionally occurs or hospitalization is needed for worsening heart failure. It has been difficult to predict such outcomes, however. Although several studies have attempted to identify prognostic factors for a poor outcome in patients with IDCM, none has revealed a factor proven to predict unequivocally the risk of cardiac events. Our present study is thus the first to show that the occurrence of pacing-induced mechanical alternans is a potential independent clinical predictor of cardiac events in patients with mild-to-moderate IDCM in sinus rhythm.

Pacing-induced mechanical alternans. We have shown that the amount of SERCA2 mRNA in LV endomyocardial biopsy specimens was decreased in IDCM patients with pacing-induced mechanical alternans compared with that in such patients without pacing-induced mechanical alternans, whereas the amount of ryanodine receptor 2 mRNA was significantly reduced in both patient groups compared with that in the control group. Because of the difficulty in obtaining appropriate specimens, few studies have investigated the cellular mechanism of mechanical alternans in the intact human heart. A reduction in the amounts of both SERCA2 and ryanodine receptor 2 mRNAs was previously described in humans with end-stage dilated cardiomyopathy at the time of heart transplantation (21,22).

Table 3. RT-PCR Analysis of the Abundance of Ca^{2+}-Handling Protein mRNAs (Normalized by the Amount of GAPDH mRNA) in Endomyocardial Biopsy Specimens

mRNA Ratio	Controls	Group A	Group B
SERCA2/GAPDH	1.24 ± 0.18	0.50 ± 0.12*	0.30 ± 0.13*†
Phospholamban/GAPDH	2.01 ± 0.69	2.13 ± 0.80	1.84 ± 0.19
Ryanodine receptor 2/GAPDH	1.45 ± 0.26	0.48 ± 0.16*	0.54 ± 0.34*
Calsequestrin/GAPDH	2.26 ± 1.75	1.61 ± 0.89	1.61 ± 1.25
Na^+-Ca^{2+} exchanger/GAPDH	2.68 ± 2.29	0.99 ± 0.84	1.37 ± 1.02
SERCA2/Na^+-Ca^{2+} exchanger	0.87 ± 0.65	1.20 ± 1.25	0.30 ± 0.20

*p < 0.05 vs. controls; †p < 0.05 vs. group A.
GAPDH = glyceraldehyde-3-phosphate dehydrogenase; RT-PCR = reverse transcription-polymerase chain reaction; SERCA2 = sarcoplasmic reticulum Ca^{2+}-ATPase.

Table 4. Univariate and Multivariate Predictors of Cardiac Events in IDCM Patients

	Univariate Analysis			Multivariate Analysis	
	Event-Free Group (n = 24)	Cardiac-Event Group (n = 10)	p Value	OR (95% CI)	p Value
Group A/group B	19/5	2/8	**0.004**	6.18 (1.31–29.2)	0.021
Age (yrs)	47 ± 13	52 ± 12	0.366		
Gender (M/F)	22/2	7/3	0.276		
LV end-diastolic dimension (mm)	63 ± 10	66 ± 7	0.290		
LV end-systolic dimension (mm)	51 ± 10	56 ± 7	0.139		
LV end-diastolic volume (ml)	195 ± 95	224 ± 97	0.442		
LV end-systolic volume (ml)	129 ± 79	161 ± 81	0.295		
LVEF (%)	38 ± 9	31 ± 7	**0.032**		
PAWP (mm Hg)	10 ± 6	18 ± 10	0.077		
Cardiac index (l min^{-1} m^{-2})	3.04 ± 0.66	2.57 ± 0.74	0.143		
Plasma BNP (pg/ml)	75 ± 78	238 ± 217	0.131		
Heart rate (beats/min)	74 ± 14	91 ± 19	**0.005**		
LV peak-systolic pressure (mm Hg)	121 ± 16	112 ± 22	0.147		
LV end-diastolic pressure (mm Hg)	11 ± 7	18 ± 10	**0.021**		
LVEDP/cardiac index (mm Hg min m^2 l^{-1})	3.83 ± 2.99	7.91 ± 5.32	**0.043**		
LV dP/dt_{max} (mm Hg/s)	1,266 ± 256	1,103 ± 208	0.083		
Peak change in LV dP/dt_{max} (%)	110 ± 11	112 ± 8	0.727		
$T_{1/2}$ (ms)	40 ± 8	43 ± 9	0.401		

Significant p values are shown in **bold** for univariate analysis.
CI = confidence interval; LVEDP = left ventricular end-diastolic pressure; OR = odds ratio; PAWP = pulmonary arterial wedge pressure. Other abbreviations as in Table 1.

Whether abnormal expression of the SERCA2 gene is responsible for mechanical alternans remains unclear. The presence of a delay between the uptake of Ca^{2+} into the sarcoplasmic reticulum and its subsequent release has been proposed to account for mechanical alternans (23–25). Our mRNA measurements do not directly reflect the Ca^{2+} uptake and Ca^{2+} release activities of sarcoplasmic reticulum in the myocardium. However, our data suggest that a decrease in the abundance of mRNAs for proteins that mediate Ca^{2+} uptake (SERCA2) or Ca^{2+} release (ryanodine receptor 2) might result in a reduction in the relative number of excitation-contraction coupling sites and in consequent dysregulation of Ca^{2+} handling by the sarcoplasmic reticulum in the failing myocardium. Such abnormal Ca^{2+} handling might substantially alter the force-frequency relation and myocardial performance.

Comparison with previous studies. Outcome can be improved in high-risk patients with CHF by treatment intensification and home-based interventions (7,26). However, there is currently no simple clinical criterion or score for predicting short-term outcome after discharge and thus for identifying patients for whom extra caution is required.

Plasma BNP level has been suggested to be a strong, independent predictor of cardiac events and sudden death in patients with CHF (27,28). A high plasma concentration of BNP before discharge was reported to be a powerful, independent marker of death or readmission in patients with decompensated CHF (7,29,30); BNP is thus now widely used as a clinical marker for differential diagnosis and management of heart failure. Patients with plasma BNP levels that do not correlate with the severity of their heart failure are encountered not infrequently, however. Several studies have suggested that BNP is substantially less accurate for detection of milder degrees of systolic dysfunction (10), which are more common than are severe forms but are also associated with increased risk. Additional studies are needed to define optimal therapy for mild asymptomatic LV systolic dysfunction (31).

Left ventricular ejection fraction has also been suggested as an independent prognostic factor (27,32,33). An LVEF of <20% was thus found to be associated with a one-year mortality of 30% in patients with dilated cardiomyopathy (4). However, other studies either did not support this finding (34,35) or showed that LVEF was less predictive than were other parameters such as transmitral inflow characteristics

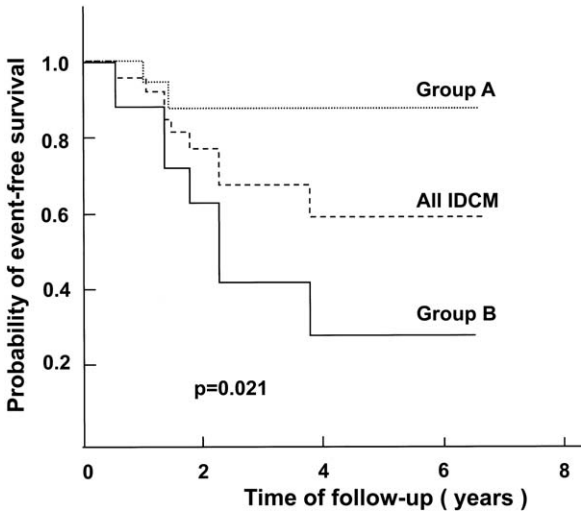

Figure 2. Cumulative probability of event-free survival calculated by the Kaplan-Meier method for all idiopathic dilated cardiomyopathy patients and patient groups A and B. The probability of event-free survival in group A was significantly greater than that in group B by the log-rank test (p = 0.021).

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(5). A limitation of these markers, however, is their load dependence, which may confound accurate assessment of LV systolic or diastolic function and limit their predictive value (36).

The patients in our study were ambulatory, had a mean LVEF of 35%, and were in sinus rhythm. They were all of New York Heart Association functional class I or II, whereas most previous studies have been based on patients of class III or IV. In addition, most previous studies have included patients with atrial fibrillation. The presence of atrial fibrillation with heart failure has been shown to be independently associated with an increased risk for mortality (16).

Our prospective study constitutes the first demonstration that the occurrence of pacing-induced mechanical alternans is a potentially important and independent prognostic predictor in clinically stable and ambulatory patients with mild-to-moderate IDCM in sinus rhythm. Our results support the notion that assessment of contractile reserve and of responses to physiological stress in the myopathic heart provides important prognostic and pathophysiological insight over and above that derived under baseline conditions. For patients with IDCM, especially those in whom cardiac catheterization is performed for diagnosis, examination for the occurrence of pacing-induced mechanical alternans may thus provide prognostic information in addition to that based on LVEF or plasma BNP concentration.

Clinical implications and study limitations. The prevalence of cardiac events or cardiac death was higher in the patients with pacing-induced mechanical alternans than in those without it in the present study. Our results should therefore facilitate the clinical identification of patients with an increased mortality and morbidity risk, as well as prove helpful in the design of future trials examining mortality in individuals with mild-to-moderate IDCM. Assessment of pacing-induced mechanical alternans in addition to routine clinical evaluation in patients with mild-to-moderate IDCM may thus contribute to stratification of patients into low- or high-risk groups.

The identification of pacing-induced mechanical alternans requires an invasive examination. This condition is therefore not amenable to repeated assessment over time, possibly representing a limitation of its prognostic utility. The small number of patients enrolled in the present study and the limited number of variables tested for prognostic merit also represent limitations to the generalizability of its findings. Further studies with larger numbers of subjects will thus be needed to confirm our present results.

Conclusions. The occurrence of pacing-induced mechanical alternans was demonstrated to be a potentially useful clinical predictor of poor prognosis in patients with mild-to-moderate IDCM in sinus rhythm. The myocardial abundance of SERCA2 mRNA was decreased in patients with pacing-induced mechanical alternans compared with that in those without it. Whether these findings will also hold for patients with more severe heart failure requires further investigation.

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